Role of Wnt Signaling in Development of Adipose Tissues and Bone

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Wnts comprise a family of secreted signaling proteins that regulate diverse developmental processes. Activation of Wnt signaling by Wnt10b inhibits differentiation of preadipocytes and blocks adipose tissue development; however, the effects of Wnt10b on other mesenchymal lineages have not been defined. To explore the physiological role of Wnt signaling in bone development, we analyzed FABP4-Wnt10b mice, which express the Wnt10b transgene in marrow. Femurs from FABP4-Wnt10b mice have almost four times as much bone in the distal metaphyses and are mechanically stronger. These mice maintain elevated bone mass at least through 23 months of age. In addition, FABP4-Wnt10b mice are protected from the bone loss characteristic of estrogen deficiency. We used pharmacological and genetic approaches to demonstrate that canonical Wnt signaling stimulates osteoblastogenesis and inhibits adipogenesis of bipotential mesenchymal precursors. Wnt10b shifts cell fate toward the osteoblast lineage by induction of osteoblastogenic transcription factors, Runx2, Dlx5, and osterix, and suppression of adipogenic transcription factors, C/EBPα and PPARγ. One mechanism whereby Wnt10b promotes osteoblastogenesis is by suppressing expression of PPARγ. Finally, Wnt10b -/- mice have decreased trabecular bone and serum osteocalcin, confirming that Wnt10b is an endogenous regulator of bone formation.